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Risk factors for poorer respiratory outcomes in adolescents and young adults born preterm

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ABSTRACT

Rationale The respiratory outcomes for adult survivors of preterm birth in the postsurfactant era are wide-ranging with prognostic factors, especially those encountered after the neonatal period, poorly understood.

Objectives To obtain comprehensive 'peak' lung health data from survivors of very preterm birth and identify neonatal and life-course risk factors for poorer respiratory outcomes in adulthood.

Methods 127 participants born ≤32 weeks gestation (64%, n=81 with bronchopulmonary dysplasia (BPD), initially recruited according to a 2 with-BPD:1 without-BPD strategy), and 41 term-born controls completed a lung health assessment at 16–23 years, including lung function, imaging and symptom review. Risk factors assessed against poor lung health included neonatal treatments, respiratory hospitalisation in childhood, atopy and tobacco smoke exposure.

Measurements and main results Young adults born prematurely had greater airflow obstruction, gas trapping and ventilation inhomogeneity, in addition to abnormalities in gas transfer and respiratory mechanics, compared with term. Beyond lung function, we observed greater structural abnormalities, respiratory symptoms and inhaled medication use. A previous respiratory admission was associated with airway obstruction; mean forced expiratory volume in 1 s/forced vital capacity z-score was −0.561 lower after neonatal confounders were accounted for (95% CI −0.998 to −0.125; p=0.012). Similarly, respiratory symptom burden was increased in the preterm group with a respiratory admission, as was peribronchial thickening (6% vs 23%, p=0.010) and bronchodilator responsiveness (17% vs 35%, p=0.025). Atopy, maternal asthma and tobacco smoke exposure did not influence lung function or structure at 16–23 years in our preterm cohort.

Conclusions Even after accounting for the neonatal course, a respiratory admission during childhood remained significantly associated with reduced peak lung function in the preterm-born cohort, with the largest difference seen in those with BPD. A respiratory admission during childhood should, therefore, be considered a risk factor for long-term respiratory morbidity in those born preterm, especially for individuals with BPD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The literature overwhelmingly reports (although largely by spirometry only) that those born preterm have impaired lung function, which is influenced by bronchopulmonary dysplasia (BPD) severity. However, BPD status alone cannot accurately predict poor long-term respiratory outcomes and risk factors encountered following the intensive neonatal period have received little focus.

WHAT THIS STUDY ADDS

⇒ Our study reports that a spectrum of impairment exists for young adults born ≤32 weeks gestation, from normal to severe. We show that, for those with BPD, a respiratory admission in childhood is a significant risk factor for reduced lung function in adolescence and young adulthood, while maternal asthma and personal history of atopy had no discernible effect.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings reveal that a childhood history of respiratory hospital admission should be a key consideration in the management of preterm children and adults. As the number of survivors of preterm birth continues to grow due to increases in the rate of preterm births, and advances in neonatal care, identifying those most at risk is key evidence needed to generate clinical guidelines for the management of these patients.

INTRODUCTION

The lungs undergo extensive growth and development throughout childhood to a 'peak' function in young adulthood. This peak is followed by a natural decline with increasing age.[1] Failure to reach an appropriate peak in lung function during young adulthood is a significant predictor of all-cause mortality[2] and a major risk factor for chronic obstructive pulmonary disease (COPD), accounting for up to half of all cases in adults.[3] Early-life respiratory infections, environmental exposures or a childhood asthma diagnosis are key contributors to a failure to reach potential peak lung function, and potentially a faster natural decline in lung function.[4]

The Early Life Origins of (respiratory) Disease pose some unique concerns for the 11% of the global population born preterm (<37 weeks gestation).[5] Life-saving treatments, such as mechanical ventilation or supplemental oxygen, can elicit injury on the incompletely developed lung of the

preterm infant. Other insults, such as early-life respiratory infections, also disproportionally affect preterm infants, likely due to an immature innate immune system and disruption to normal immune development.[6 7] In children with bronchopulmonary dysplasia (BPD), antenatal[8] and personal[9] smoke exposure are associated with lung function decline, while secondhand smoke exposure is associated with increased hospital admissions.[10] Modifiable postnatal factors are likely to contribute to decreased peak lung function in a cumulative way, and increase respiratory morbidity and mortality throughout adult life.[11] Avoiding a 'second hit' to the respiratory system has been postulated to be central to mitigating adult respiratory disease following preterm birth.[12]

Several studies have established that survivors of preterm birth have altered lung structure, increased respiratory symptoms and low lung function (although largely by spirometry only) throughout life[13–16] and that these deficits are exacerbated by diagnosis of chronic lung disease of infancy, bronchopulmonary dysplasia (BPD).[17–19] Further, it has been shown by our group (in the same cohort) and others, that lung function trajectories move further from predicted throughout childhood[8] and adolescence.[9] However, identifying risk factors, especially those encountered following the intensive neonatal period, for poor long-term respiratory outcomes have received little focus.

Comprehensive assessments of lung structure, function and symptoms profiles near 'peak' are of particular value, and are rare in modern survivors of very preterm birth.[20 21] This study aimed to provide a comprehensive cross-section of lung health in very preterm born adolescents and young adults (near 'peak'), and importantly, assess the role of antenatal, neonatal and early childhood exposures on peak lung function, lung structure and respiratory symptoms. We hypothesised that preterm birth would be associated with reduced lung function and ongoing respiratory morbidity in young adulthood and that this would be worse for those with early-life risk factors, including increased respiratory support, respiratory hospitalisation and exposure to tobacco smoke.

METHODS

Participants

Adolescents and young adults from the pre-existing Western Australian Lung Health in Prematurity cohort[8 13 16] were invited to attend a research appointment aged 16–23 years. Detailed information on the cohort has been previously published.[13] Briefly, the preterm group were born at King Edward Memorial Hospital ≤32 weeks gestation between 1997 and 2003. BPD was defined as at least 28 days supplemental oxygen requirement as assessed at 36 weeks postmenstrual age.[22] In the cohort, there is a deliberate recruitment strategy of 1 term: 1 preterm (without BPD): 2 preterm (with BPD). The incidence of BPD in infants born at 32 weeks' gestation or earlier during these birth years is 28% in Western Australia.[8] Therefore, the proportion of those with of BPD in this cohort (67%) is over double that expected in the general population born 32 weeks gestation or less. Due to this recruitment strategy, the overall preterm cohort is born at an earlier gestation and lower birth weight than would be expected in the general population.[16]

We have previously shown the subgroups with and without BPD are representative of the corresponding populations in the local area, born during these birth years.[13] Briefly, in these subgroups, there is no difference in birth weight or days of supplemental oxygen compared with the corresponding eligible populations. While gestational age (GA) is not different for preterm participants with BPD, those without BPD had a slightly lower GA than the non-recruited cohort.[13]

Term controls were recruited at earlier cohort follow-ups,[13 16] briefly they were born at ≥37 weeks gestation, with no history of cardiopulmonary disease or recurrent respiratory symptoms at time of recruitment. Written informed consent and assent (where appropriate) was obtained from the participant (and their guardian where appropriate).

Assessment of lung function

Assessment of lung function included spirometry, diffusing capacity for the lung, whole body plethysmography, multiple breath washout, fractional exhaled nitric oxide and oscillometry carried out according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines. The bronchodilator response was assessed by spirometry following the administration of 400 µg salbutamol via spacer. Where possible, lung function outcomes were expressed as z-scores (additional detail on lung function methodology is provided in online supplemental data).

Assessments of lung structure

CT images of the chest were acquired during inspiration and expiration in both term-born and preterm-born participants. Inspiratory and expiratory volumetric images spanned from the lung apex to the diaphragm at ultra-low radiation dose (dose length product: 8 mGy×cm, regardless of age) (Somatom Definition Force, Siemens, Erlangen). The chest CT images were consensus scored using a modification of the scoring system described by Aukland *et al*.[13 23] Extent scores are directly related to the number of affected lobes (maximum=6) except for collapse/consolidation (maximum=2) with a possible total CT score of 50. Scorers were blinded to all participant information. A random subset of CT scans (n=22) were rescored within 6 months, by the same observers. Cronbach's alpha and the intraclass correlation coefficient (ICC) estimate with 95% CIs were calculated using IBM SPSS Statistics for Windows, V.27.0, based on a single-rating, absolute-agreement, 2-way mixed-effects model.

Assessment of risk factors for poor lung health

A history of household tobacco smoke exposure, respiratory hospitalisation, maternal asthma, personal asthma, eczema or hay fever were assessed via a questionnaire, with a positive history at any of the cohort follow-ups included in the analysis.[24] Additionally, respiratory symptoms in the 3 months prior to the visit was assessed using the same questionnaire. Neonatal data extracted from medical records included GA, birth anthropometrics, antenatal and neonatal steroid exposure, confirmed sepsis during neonatal intensive care unit (NICU) admission, number of surfactant doses, days of supplemental oxygen, mechanical ventilation and continuous positive airway pressure (CPAP).

Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, V.27.0. Data were assessed for normality using the Shapiro-Wilk test and reported as means and SD for normally distributed data and medians and IQR for non-normally distributed data. Differences between groups were assessed by paired T-test, Mann-Whitney U test, one-way analysis of variance or the Kruskal Wallis test, as appropriate. For normally distributed data, Bonferroni correction was applied to account for possible type 1 errors due to multiple testing; for non-parametric data, pairwise

comparisons were used. χ^2 analysis was used for differences in proportion between groups.

The association between predictors (neonatal treatments, respiratory admissions, CT scores) and lung function was investigated using univariate and multivariable linear regression models. Multivariable regression models were built using all independent variables, which were entered into the model individually and the significance of the change in R^2 at each step was analysed. The effect size was defined as the unstandardised β coefficient. Normal distribution of residuals was confirmed by visualisation of histogram and Q-Q plots. To evaluate the association between neonatal factors and respiratory admissions with young adult CT scores, univariate and multivariable negative binomial regression was performed. Dichotomous outcomes with dichotomous predictors are analysed using logistic regression and ORs are reported.

RESULTS

Study participants at follow-up visit

A total of 168 participants (41 term; 127 preterm) were included (online supplemental figure E1) at a mean (SD) age of 19.31 (1.39). Of the preterm participants, 19 had mild BPD while 62 had moderate-to-severe BPD.[22] Participant demographics are shown in table 1. Recent respiratory symptoms, respiratory-based hospitalisations, exposure to tobacco smoke and atopy

Table 1 Participant demographics and risk factors at adolescent/young adult follow-up visit

	Term	Preterm	Preterm No BPD	BPD
Participants, n	41	127	46	81
Sex				
Females, n (%)	19 (46)	56 (44)	17 (37)	39 (48)
Males, n (%)	22 (54)	71 (56)	29 (63)	42 (52)
Age (years)	19.3 (1.5)	19.3 (1.4)	19.0 (1.2)	19.5 (1.4)
Height (cm)	175.4 (9.6)	**169.0 (9.7)***	171.5 (9.4)	**167.5 (9.5)***
Weight (kg)	70.2 (14.7)	65.9 (17.6)	70.6 (22.3)	63.2 (13.6)
BMI	22.7 (3.9)	22.8 (4.5)	23.6 (5.2)	22.4 (4.0)
SpO_2 (%)	98 (1)	98 (1)	98 (1)	98 (1)
Heart rate (bpm)	76 (10)	79 (12)	75 (11)	**81 (12)†**
Systolic blood pressure (mm Hg)	125 (10)	126 (12)	129 (12)	125 (12)
Diastolic blood pressure (mm Hg)	72 (8)	71 (9)	71 (10)	71 (9)
Symptoms in the 3 months prior to test visit, n (%)				
Asthma medication	0 (0)	**21 (16.5)***	**8 (17.4)***	**13 (16.0)***
Wheeze	1 (2.4)	15 (11.8)	5 (10.9)	10 (12.3)
Wheeze during exercise	2 (4.9)	**23 (18.1)***	**9 (19.6)***	**14 (17.3)***
Cough	20 (48.8)	64 (50.4)	17 (37.0)	**47 (58.0)†**
Rattle	2 (4.9)	21 (16.5)	2 (4.3)	**19 (23.5)*†**
Shortness of breath	5 (12.2)	**37 (29.1)***	12 (26.1)	**25 (30.9)***
Reported respiratory hospitalisations (lifetime)				
Respiratory hospitalisation, n (%)	3 (7.3)	**63 (49.6)***	**15 (32.6)***	**48 (59.3)*†**
No of respiratory hospitalisations, median (IQR)	0 (0–0)	**0 (0–1)***	0 (0–1)	**1 (0–1)***
No of respiratory hospitalisations, range	0–2	0–12	0–10	0–12
Smoking, n (%)				
Ever smoker	2 (4.9)	6 (4.7)	3 (6.5)	3 (3.7)
Household smoke exposure	8 (19.5)	**59 (46.5)***	**23 (50.0)***	**36 (44.4)***
Asthma/atopy, n (%)				
Asthma ever	5 (12.2)	**67 (52.8)***	**29 (63.0)***	**38 (46.9)***
Hay fever ever	10 (24.4)	**58 (45.7)***	**22 (47.8)***	**36 (44.4)***
Eczema ever	15 (36.6)	44 (34.6)	17 (37.0)	27 (33.3)
Atopy (hay fever or eczema ever)	17 (41.5)	**77 (60.6)***	**29 (63.0)***	48 (59.3)
Physician diagnosed maternal asthma	4 (9.8)	29 (22.8)	**12 (26.1)***	17 (21.0)

Participant demographics at the time of testing are presented as mean (SD) unless otherwise indicated. The 'preterm' group is composed of all preterm participants, recruited using a deliberate 1 preterm without BPD: 2 preterm with BPD strategy.
Bold font indicates statistical significance.
*p<0.05 compared with term-born group.
†p<0.05 compared with no-BPD group.
BMI, body mass index; BPD, bronchopulmonary dysplasia; SpO2, peripheral oxygen saturation.

Table 2 Neonatal information for preterm participants at adolescent/young adult follow-up

		Preterm	
	Preterm	**No BPD**	**BPD**
Participants, n	127	46	81
Gestational age (PMA)	27.0 (25.0, 29.4)	29.9 (28.4, 30.5)	**25.7 (24.9, 27.0)***
Birth weight (g)	930 (750, 1195)	1323 (1165, 1574)	**825 (685, 935)***
Birth weight z-score (mean, SD)	−0.16 (0.89)	−0.12 (0.83)	−0.19 (0.93)
Duration of oxygen supplementation (days)	57 (3, 95)	1 (0, 3.3)	**91 (62.5, 104)***
Duration of mechanical ventilation (days)	5 (0.5, 28)	0 (0, 1.2)	**20 (5, 36.5)***
Duration of CPAP (days)	6 (1, 19.6)	1 (0, 3.6)	**14 (5.1, 24.8)***
Surfactant administered, n (%)	94 (74.0)	22 (47.8)	72 (88.9)
Antenatal steroids, n (%)	100 (78.7)	35 (76.1)	65 (80.2)
Postnatal steroids, n (%)	35 (27.6)	4 (8.7)	31 (38.3)

Continuous neonatal variables are presented as median (IQR), except birth weight z-score (mean, SD). Birthweight z-score was calculated from Fenton growth charts for preterm infants.[45] Antenatal steroids includes those who received the intervention a minimum of 24 hours prior to delivery only. The 'preterm' group is composed of all preterm participants, recruited using a deliberate 1 preterm without BPD: 2 preterm with BPD strategy.
Bold font indicates statistical significance.
*Represents significant difference between the preterm groups with and without BPD (p<0.05).
BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; PMA, postmenstrual age.

were all higher in the preterm born population (table 1). Asthma diagnosis (ever), asthma medication use and exercise-induced wheeze in the past 3 months were increased in both the no-BPD and BPD groups compared with term-born controls. Recent cough, rattle and shortness of breath were increased in the BPD group only (table 1).

We did not observe evidence of selection bias when we compared data from participants that did and did not take part in this adolescent/young adult follow-up. The preterm participants returning for this follow-up were born at a median (IQR) gestation of 27.0 (25.0–29.4) weeks, comparable to the wider cohort (p=0.255). Other neonatal information describing the preterm cohort are presented in table 2. We report no difference in neonatal course (eg, proportion preterm with BPD, 45.7% vs 41.5%, p=0.866) or lung function (eg, forced expiratory volume in 1 s (FEV_1) at 11 years; mean difference −0.03 z-scores, 95% CI −0.47 to 0.41, p=0.878) between preterm-born participants who did, and did not attend on this occasion.

Lung function in adolescents and young adults born preterm

Forced flows and volumes

No difference in forced vital capacity (FVC) was observed, however, airflow obstruction was evidenced by reduced spirometric values (FEV_1, FEV_1/FVC, forced expiratory flow $(FEF)_{25-75}$, FEF_{75}) in young adults born preterm, with increased severity in those with BPD (table 3). Abnormally low lung function (defined as FEV_1, FEV_1/FVC, $FEF_{25–75}$ or FEF_{75} ≤−1.64 z-scores) was observed in 6 of the term controls (15.8%), 15 (35.7%) of the preterm group without BPD, and 39 (54.2%) of those with BPD (p<0.001). Baseline FEV_1 was less than −1.64 z-scores in 2 of the term controls (5.0%), 6 (14.0%) of the preterm group without BPD and 24 (30.8%) of those with BPD (p=0.002). The corresponding values for FEV_1/FVC<−1.64 z-scores were: term controls (n=4, 10.5%), preterm group without BPD (n=13, 31.0%) and preterm with BPD (n=30, 41.7%, p=0.004).

Bronchodilator responsiveness

Of the 29 young adults born preterm with a baseline FEV_1<−1.64 z-scores (and acceptable pre- and post-bronchodilator spirometry), 19 (65.5%) had a significant bronchodilator response, while the remaining 10 (34.5%) did not. A bronchodilator response was observed in 7.7% of term controls, 16.7% of those preterm without BPD, increasing to 31.2% in those with BPD (p=0.010).

Gas exchange

Gas exchange (diffusing capacity of the lung for carbon monoxide (DLCO)) was reduced in the preterm cohort compared with term-born controls, and worst in those with BPD, with a mean DLCO z-score difference of −0.63 (95% CI −0.25 to −1.01) and KCO z-score difference of −0.55 (95% CI −0.21 to −0.90). There was no observed difference in alveolar volume in those born ≤32 weeks GA (table 3).

Static lung volumes by whole body plethysmography

Young adults with BPD had an increased residual volume (RV) and RV as a percentage of total lung capacity (RV/TLC) compared with term-born controls, suggestive of gas trapping (table 3). There were no differences observed in other measures of static lung volumes, including TLC and functional residual capacity in those born preterm (table 3).

Ventilation homogeneity by multiple breath washout

There was increased ventilation inhomogeneity in those born preterm compared with term-born controls, evidenced by increased Lung Clearance Index and the first and second moment ratios of the gas washout (M1/M0 and M2/M0, respectively). The greatest increase in ventilation inhomogeneity was observed in the BPD group (table 3).

Airway inflammation

Fractional exhaled nitric oxide was lower in the preterm group with BPD, compared with term-born controls (p=0.03) (table 3).

Respiratory system mechanics (by plethysmography and oscillometry)

Young adults born preterm had poorer peripheral lung mechanics than term-born controls, which was worst in those with BPD, evidenced by decreased respiratory system reactance

Table 3 Lung function in term and very preterm-born adolescents and young adults

			Preterm	
	Term controls (reference)	Preterm	No-BPD	BPD
Forced flows and volumes (spirometry)				
n successful	40	121	43	78
FEV_1 z-score	−0.03 (1.14)	**−0.88 (1.16)***	−0.48 (1.10)	**−1.10 (1.14)*†**
FEV1 z-score post-BD	0.34 (1.12)	**−0.28 (1.02)***	0.00 (1.07)	**−0.43 (0.97)***
n successful	38	113	41	72
FVC z-score	0.09 (1.07)	−0.01 (1.02)	0.21 (1.03)	−0.14 (1.01)
FEV_1/FVC z-score	−0.19 (1.08)	**−1.17 (1.12)***	**−0.99 (1.14)***	**−1.27 (1.10)***
FEF_{25-75} z-score	−0.27 (1.11)	**−1.29 (1.15)***	**−0.98 (1.15)***	**−1.47 (1.13)***
Bronchodilator assessment, n	39	119	42	77
No with BDR	3 (7.7%)	**31 (26.1%)***	7 (16.7%)	**24 (31.2%)***
Gas exchange (DLCO)				
n successful	41	120	45	75
DLCO z-score	1.48 (0.97)	**0.85 (1.08)***	1.06 (1.11)	**0.73 (1.05)***
VA z-score	0.74 (0.88)	0.64 (1.18)	0.71 (1.15)	0.60 (1.20)
KCO z-score	0.89 (0.85)	**0.33 (1.01)***	0.49 (1.07)	**0.24 (0.97)***
Lung volumes (whole body plethysmography)				
n successful	40	123	44	79
TLC z-score	0.27 (0.70)	0.28 (0.82)	0.34 (0.81)	0.25 (0.83)
FRC z-score	0.42 (0.69)	0.55 (0.92)	0.42 (0.89)	0.62 (0.93)
RV z-score	0.47 (0.53)	0.69 (0.79)	0.51 (0.74)	**0.79 (0.81)***
RV/TLC (%) z-score	0.50 (0.73)	0.77 (0.93)	0.52 (0.85)	**0.91 (0.95)***
Respiratory system mechanics (oscillometry)				
n successful	41	125	45	80
Rrs_5 z-score	1.25 (0.87)	1.33 (1.18)	1.20 (1.46)	1.40 (0.98)
Fres z-score	1.13 (1.04)	**1.90 (1.42)***	1.42 (1.42)	**2.17 (1.36)*†**
AX z-score	1.25 (0.85)	**1.92 (1.15)***	1.61 (1.23)	**2.10 (1.08)*†**
Xrs_5 z-score	0.75 (0.92)	**1.36 (1.49)***	1.04 (1.41)	**1.54 (1.51)***
Rrs_{5-20} ($cmH_2O.s/L$)	0.10 (0.34)	**0.51 (0.81)***	0.40 (0.77)	**0.57 (0.83)***
Median (IQR)				
Airway Inflammation				
n successful	41	125	45	80
FeNO (ppm)	19 (12, 25)	15 (10, 26)	19 (12, 32)	**13 (10, 19)†**
Ventilation distribution (multiple breath wash-out)				
n successful	36	97	40	**57***
LCI	6.54 (5.99, 7.19)	**7.26 (6.46, 8.19)***	7.14 (5.96, 7.79)	**7.39 (6.63, 8.49)***
MR1 (M1/M0)	1.79 (1.50, 1.97)	**1.94 (1.57, 2.19)***	1.94 (1.52, 2.15)	**1.94 (1.61, 2.34)***
MR2 (M2/M0)	5.68 (4.16, 6.98)	**6.92 (4.59, 8.85)***	6.90 (4.14, 8.57)	**7.02 (4.70, 10.11)***
Airway resistance (plethysmography)				
n successful	40	119	43	76
sGaw (1 /s*cmH_20)	0.20 (0.17, 0.25)	**0.15 (0.11, 0.23)***	0.17 (0.11, 0.25)	**0.15 (0.11, 0.20)***

Data are presented as mean (SD) unless otherwise indicated, except for the number of successful tests. The 'preterm' group is composed of all preterm participants, recruited using a deliberate 1 preterm without BPD: 2 preterm with BPD strategy.
Bold font indicates statistical significance.
*p<0.05 compared with term-born group.
†p<0.05 compared with no-BPD group.
AX, area under the reactance curve; BD, bronchodilator; BDR, bronchodilator response; BPD, bronchopulmonary dysplasia; DLCO, diffusing capacity of the lung for carbon monoxide; FEF_{25-75}, forced expiratory flow at 25%–75% of the pulmonary volume; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; Fres, resonant frequency; FVC, forced vital capacity; KCO, carbon monoxide transfer coefficient; LCI, Lung Clearance Index; MR1/2, moment ratio 1/2; Rrs_{5-20}, difference in respiratory system resistance between 20 and 5 Hz; RV, residual volume; sGaw, specific airway conductance; TLC, total lung capacity; VA, alveolar volume; Xrs_5, respiratory system reactance at 5 Hz.

at 5 Hz (Xrs_5), area under the reactance curve (AX) and resonant frequency (Fres) z-scores (table 3). Respiratory resistance z-scores measured by oscillometry were not significantly increased in those born preterm. However, the plethysmographic measure of airway resistance that is independent of lung volume (sGaw) revealed decreased airway conductance in those born ≤32 weeks GA, which was further decreased in those with BPD (table 3).

Lung structure in preterm adolescents and young adults

Structural abnormalities were present in 88% of adolescents and young adults born ≤32 weeks gestation, increasing to 92% in the BPD group (p=0.047). Of note, structural abnormalities were also present in 61% of the term-born control group, however, were more extensive in those born 32 weeks gestation or less. In those with BPD, structural abnormalities were more extensive; total scores ranged from 0 to 16 in those without BPD, increasing to 0–22 in those with BPD, out of a maximum score of 50[13 23] (see table 4 for median and IQR).

Linear and triangular pleural opacities and elicitation and/or an exaggeration of decreased pulmonary attenuation during expiration were the most commonly observed abnormalities (observed in 37% and 69% of the preterm cohort, respectively), and were more prevalent and severe in those with BPD. Bronchial wall thickening and decreased pulmonary attenuation during inspiration were also increased in those born very preterm (table 4).

The intraobserver reliability of CT scorers was excellent with an absolute agreement ICC of 0.89 (95% CI 0.69 to 0.96, p<0.001) and Cronbach's alpha of 0.95.

Association between lung structure, function and symptoms in preterm-born adolescents and young adults

Airway obstruction was observed in preterm individuals with more extensive structural abnormalities (online supplemental table E1); for example, FEV_1 decreased −0.1 z-scores for every 1 unit increase in the total CT score (95% CI −0.06 to −0.14). This association was weak (R^2=0.164) although highly statistically significant (p<0.001, figure 1). Similarly, adolescents and young adults born very preterm with wheeze during exercise (n=23, 18.1%), had increased airflow obstruction; the mean difference in FEV_1/FVC ratio was 0.544 z-scores (95% CI 0.076 to 0.101, p=0.024). Additional associations between individual lung function measures and structural abnormalities are presented in online supplemental tables E1–E9.

Neonatal factors associated with impaired lung function and structure in adolescence and young adulthood

Univariate analyses relating neonatal factors (including gestation, birth weight z-score, days of supplemental O_2, mechanical ventilation, CPAP, surfactant doses, antenatal steroids, postnatal steroids, etc) to each lung function or structure outcome are presented in online supplemental tables E10–E17. Univariate analysis revealed multiple associations between neonatal factors and adolescent/young adult lung function, however, the associations were attenuated when confounders were adjusted for. This is with the exception of increased RV and RV/TLC in those who had received longer durations of mechanical ventilation, with an effect size of 0.13 z-score change in RV/TLC for every additional 1 week of mechanical ventilation (β=0.019, 95% CI 0.003 to 0.035, p=0.021, online supplemental table E12). Negative binomial multivariable regression analysis also showed that increased requirement for supplemental O_2, mechanical ventilation or postnatal steroids, as well as a respiratory admission following discharge from the NICU, were risks for a higher peribronchial thickening score during adolescence or young adulthood (online supplemental table E17).

Table 4 The presence and extent of chest CT abnormalities in adolescents and young adults born very preterm

	Term (n=38)	Preterm (n=125)	Preterm without BPD (n=46)	Preterm with BPD (n=79)
Linear/triangular subpleural opacities				
Presence, n participants (%)	16 (42%)	**84 (67%)***	22 (48%)	**62 (79%)*†**
Extent (CT score) (IQR)	0 (0–1)	**2 (0–4)***	0 (0–2)	**2 (1–4)*†**
Decreased pulmonary attenuation—inspiration				
Presence	0 (0%)	**14 (11%)***	2 (4%)	**12 (15%)***
Extent	0 (0–0)	**0 (0–0)***	0 (0–0)	**0 (0–0)*†**
Decreased pulmonary attenuation—expiration				
Presence	13 (34%)	**86 (69%)***	**26 (57%)***	**60 (76%)*†**
Extent	0 (0–1)	**2 (0–4)***	**1 (0–4)***	**2 (1 – 4)*†**
Decreased bronchial: arterial ratio				
Presence	0 (0%)	3 (2%)	2 (4%)	1 (1%)
Extent	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Bronchiectasis				
Presence	2 (5%)	5 (4%)	3 (7%)	2 (3%)
Extent	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Bronchial wall thickening				
Presence	0 (0%)	**18 (14%)***	4 (9%)	**14 (18%)***
Extent	0 (0–0)	**0 (0–0)***	0 (0–0)	**0 (0–0)***
Bullae				
Presence	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Extent	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Emphysema				
Presence	0 (0%)	4 (3%)	0 (0%)	4 (5%)
Extent	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Collapse/consolidation				
Presence	1 (3%)	9 (7%)	3 (7%)	6 (8%)
Extent	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Structural abnormalities on chest CT				
Presence, n participants (%)	23 (61%)	**110 (88%)***	**37 (80%)***	**73 (92%)*†**
Total CT score	1 (0–2)	**4 (2–8)***	**3 (1–6)***	**5 (3–9)*†**

Presence indicates the number (%) of preterm young adults with the structural abnormality described. Extent scores were derived according to a modification of the scoring matrix by Aukland *et al*[23] where scores are directly related to the number of affected lobes (maximum=6) except for collapse/consolidation (maximum=2) with a possible total CT score of 50. Extent scores are expressed as median (IQR). The 'preterm' group is composed of all preterm participants, recruited using a deliberate 1 preterm without BPD: 2 preterm with BPD strategy.
Bold font indicates statistical significance.
*p<0.05 compared with term-born group.
†p<0.05 compared with no-BPD group.
BPD, bronchopulmonary dysplasia.

Lifetime exposures are associated with impaired respiratory function, structure and symptoms in adolescents and young adults

Smoking

The number of 'ever smokers' was not different between the term and preterm groups (p=0.968), with less than 5% of both groups reporting a history of smoking (table 1). Individuals born preterm who reported personal or household exposure to tobacco smoke did not have reduced lung function or increased

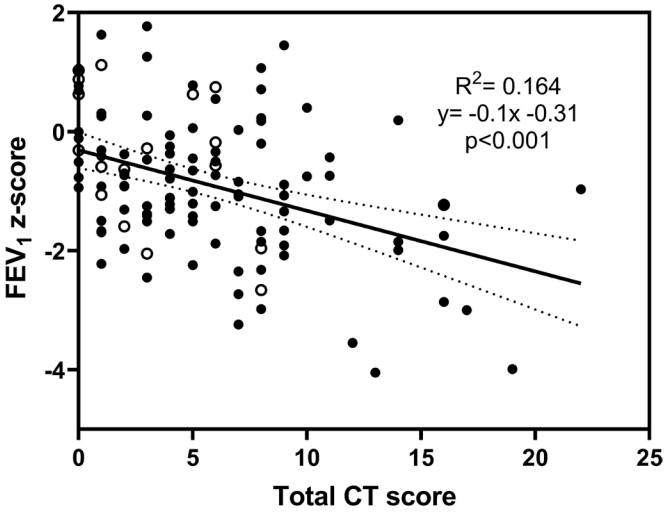

Figure 1 Lung structure abnormalities are related to lung function in preterm adolescents and young adults. FEV_1 z-score is plotted against total CT score for preterm adolescents and young adults with (closed-circle) and without (open-circle) bronchopulmonary dysplasia. Linear regression analysis is displayed, with 95% CIs (dotted lines). FEV_1, forced expiratory volume in 1 s.

structural lung damage compared with those not reporting tobacco smoke exposure (eg, figure 2).

The reporting of respiratory symptoms at rest was increased in those who had experienced household exposure to tobacco smoke (46% vs 73%, p=0.002), primarily attributable to the increased prevalence of cough (41% vs 61%, p=0.026).

Respiratory admissions are associated with respiratory structure, function and symptoms in adolescents and young adults

There was a 10-fold greater risk of a respiratory admission during childhood in those born very preterm, compared with term (OR 10.172, 95% CI 2.958 to 34.977, p<0.001). Respiratory admissions were overwhelmingly reported in childhood; all except one respiratory admission was recorded at the 9–12 years follow-up or earlier.[13] Rates of respiratory admission to hospital, were 32.6% and 59.3% in those without and with BPD, respectively (p<0.001). Additionally, those with BPD had more respiratory admissions per person (p=0.021); 22.2% (n=18) had 3 or more admissions, compared with 13.0% (n=6) in the preterm group without BPD.

In those born preterm, spirometry outcomes were reduced in those with a previous respiratory admission. Mean FEV_1/FVC was 0.61 z-scores lower in those born preterm with a respiratory admission (95% CI 0.21 to 1.02, p=0.003) and this difference was greatest in those with BPD (−0.74 z-scores, 95% CI −0.24 to −1.24, p=0.004) (figure 2). When adjusted for collinearities between respiratory admissions and neonatal factors, admissions remained significant with an effect size of −0.561 z-scores (95% CI −0.998 to −0.125, p=0.012, online supplemental table E10). A positive bronchodilator response was observed in 35.0% of those with a respiratory admission, compared with 16.9% without (p=0.025).

The presence of peribronchial thickening on chest CT was increased in those who reported a previous respiratory hospitalisation (6% vs 23%, p=0.010), as was the incidence of those reporting daytime wheeze (5% vs 18%, p=0.022), cough (36% vs 59%, p=0.010) or 'rattle' (5% vs 24%, p=0.002) in the past 3 months.

Asthma and atopy associations with lung function and structure in adolescence and young adulthood

Participant eczema/hay fever

Term-born participants with a history of atopy (eczema or hay fever ever) (n=17, 41.5%), had a reduced FEV_1/FVC z-score (mean difference −0.729, 95% CI −0.032 to −1.425, p=0.041). No difference in FEV_1/FVC was observed in those born preterm with (n=77, 60.6%) and without atopy (mean difference 0.047, 95% CI −0.382 to 0.477, p=0.948). No other lung function, structure or symptoms outcomes were different between atopic participants and non-atopic participants.

Previous asthma diagnosis

A previous respiratory admission was a risk factor for an asthma diagnosis (OR 3.12, 95% CI 1.51 to 6.45); 66.6% (n=42) of those reporting a previous respiratory admission had received an asthma diagnosis, compared with 39.1% (n=25) of those who had not. Those born preterm with a previous asthma diagnosis had a greater degree of airflow obstruction (FEV_1/FVC mean difference −0.609 z-scores, 95% CI −0.206 to −1.013), a greater extent of bronchiectasis (p=0.032) and peribronchial thickening (p=0.017) and increased prevalence of wheeze, both at rest (3% vs 19%, p=0.005) and with exertion (8% vs 27%, p=0.007).

Maternal asthma

There was no difference in any lung function outcomes, CT scores or respiratory symptoms in individuals with a maternal asthma history (eg, figure 2).

DISCUSSION

Here, we present a comprehensive assessment of lung function, symptoms and structure at close to peak function in contemporary survivors of very preterm birth, that is, following the routine introduction of exogenous surfactant in the NICU during the early 1990s. We demonstrated a significant burden of respiratory disease, including airflow limitation prebronchodilator and post-bronchodilator, reduced gas transfer, ventilation inhomogeneity, increased symptoms and structural lung abnormalities, with the worst deficits observed in those with BPD. Importantly, we identify risk factors for lower than predicted peak lung function in this population, finding that early-life respiratory admissions were associated with reduced peak lung function and increased peribronchial thickening. A history of maternal asthma or atopy (hay fever or eczema ever) had no discernible effect on later lung function for those born ≤32 weeks gestation.

We report clinically relevant lung function impairment in adolescent and young adult survivors of very preterm birth, which is exacerbated in those with BPD. These findings extend previous studies.[25–28] The existing literature in adolescent and young adult survivors of preterm birth has been difficult to interpret to date[29] for reasons that include small sample size, a lack of suitable control groups and limited examples of comprehensive physiological testing. Further, previous studies have largely composed of adolescents and young adults who were born in the presurfactant era. Contemporary survivors with BPD are born at much earlier gestation and have a vastly different pulmonary pathophysiology compared with 'old BPD'.[30] This lack of clear evidence about the long-term impact of contemporary preterm birth has been cited as a key contributor to a clinician 'blind spot', where few adult respiratory physicians routinely consider early-life factors (ie, preterm birth) during patient assessment.[31] Such suggestions are concerning as failure to achieve optimal

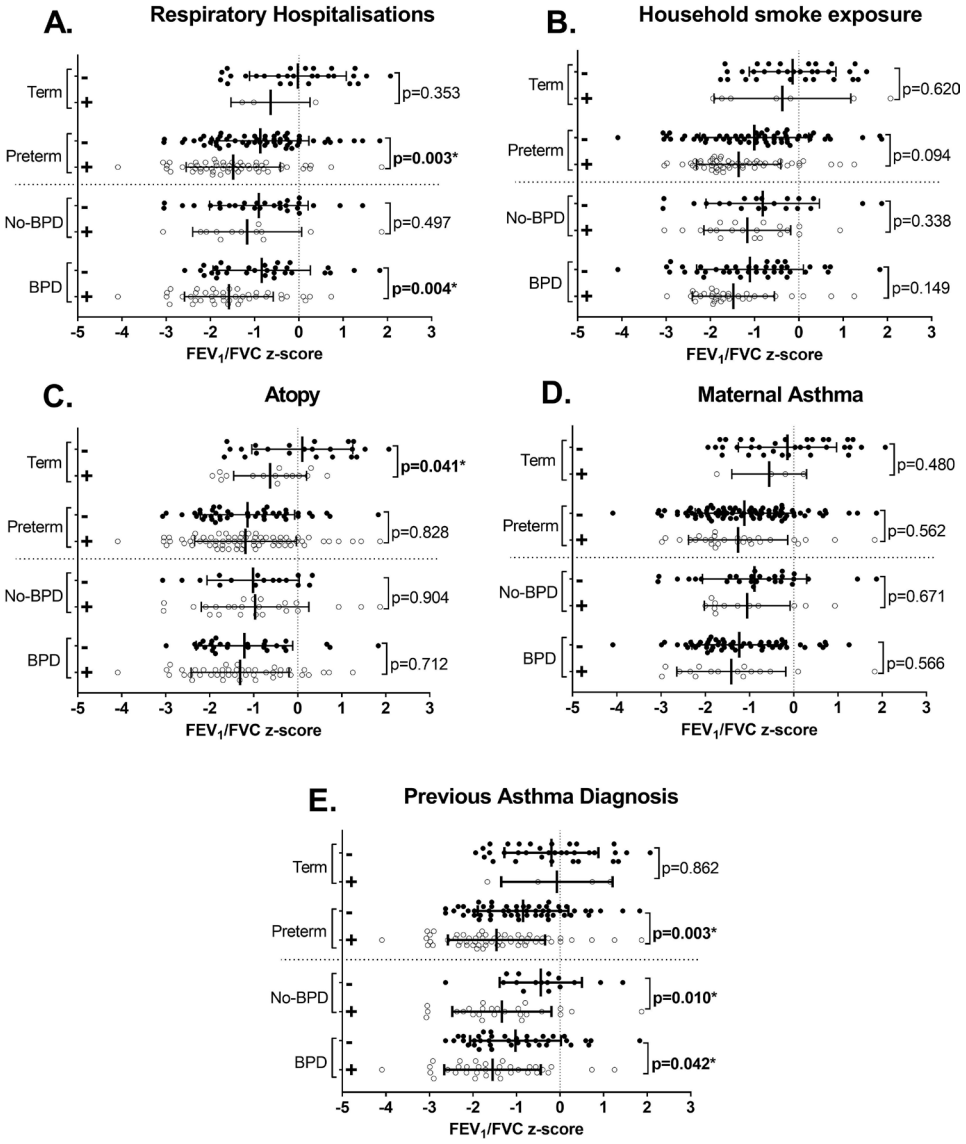

Figure 2 Risk factors influence lung function at age 19. The association between (A) respiratory hospitalisations, (B) household smoke exposure, (C) atopy, (D) maternal asthma and (E) a previous asthma diagnosis, and airway obstruction (FEV_1/FVC z-score) in young adults born preterm (no-BPD and BPD), and term-born controls. Error bars represent mean±SD. *Represents significant difference between the with (+, open circle)) and without (–, closed circle) (factor) for each group. BPD, bronchopulmonary dysplasia; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

peak lung function, and a vulnerability to accelerated decline, has raised concerns that those born early are at risk of developing a COPD-like phenotype in early adulthood.[32] Indeed, studies suggest that those born prematurely have >2 fold increased risk of COPD in middle age[33] and the mortality risk remains increased across the entire lifespan.[34] Of significant note, 10% of our cohort had persistent airflow obstruction (FEV_1/FVC<LLN), after the administration of a bronchodilator, satisfying the spirometric diagnostic criteria for COPD. This rate is twice that observed for COPD in Australia in those over 45 years of age.[35]

The potentially increased risk of COPD after preterm birth is especially pertinent for those exposed to tobacco smoke. Concerningly, in the preterm group we observed rates of household smoke exposure twice that of the control group, an observation likely linked to the interplay between low socioeconomic status, cigarette smoking and preterm birth.[36] Urinary cotinine analysis was not performed to confirm smoking status, however, a personal history of smoking has previously been found to be reliable in this population.[37] While we failed to observe a reduced FEV_1 in those with tobacco smoke exposure (p=0.094, figure 2), we have previously noted in the same cohort that household tobacco smoke exposure was associated with increased declines in lung function throughout childhood.[8] Similarly, Doyle *et al* observed negligible difference in lung function between smokers and non-smokers aged 18, however, crucially showed personal smoking is associated with lung function decline from 8 to 18 years.[9] Continued follow-up of preterm born cohorts including smoking status will be essential to fully understand the implications of tobacco smoke exposure over time in this at-risk population.

We show that structural abnormalities are very common (88%) near peak lung health in survivors of contemporary preterm birth, the proportion and extent of which is increased in those with BPD. Consistent with the limited number of chest CT imaging studies,[23 38] we report that linear and triangular opacities were the most commonly observed abnormality. However, a particular strength of this study is the inclusion of

imaging healthy term-born controls, who also have high rates of linear and triangular opacities, raising the question about their importance as an 'abnormality'. We report relatively low rates of emphysema in this population of adolescents and young adults with BPD (5%), compared with individuals of the same age, from the same centre born in the presurfactant era (47%).[38] However, this difference may also be explained by potential recruitment bias in the previous study, with some subjects recruited from respiratory clinics.

In this study factors beyond the NICU were associated with suboptimal peak lung function for survivors of preterm birth. The European Respiratory Society recently published the first guidelines for the long-term clinical management of those with BPD.[39] One of the eight critical questions identified pertained to the role of early-life infection (day care attendance), however, no articles were available to guide recommendations. Our data reiterate the importance of avoiding a 'second hit' to the respiratory system to improve adult outcomes.[12] We show that a previous (infection related) respiratory admission was more impactful on lung health at age 19 years than neonatal factors, although we could not exclude that a respiratory admission after discharge could be a marker for pre-existing, premorbid pulmonary status. Notwithstanding, our findings raise hope for prophylactic therapeutic or life-style intervention, but also concern that those born ≤32 weeks gestation, especially those with BPD, are susceptible to further lung damage after leaving the NICU. Of concern, rehospitalisation rates for preterm babies with a respiratory virus are high (~40% of the preterm population, including ~65% of those with BPD),[40] with similar rates of rehospitalisation in our cohort (59.3% in those with BPD). Early-life viral infections are associated with increased likelihood of later wheezing, asthma and reduced lung function in the term-born population,[4 41 42] but the sparse studies after preterm birth have only focused on small numbers with RSV-related hospitalisations during infancy.[43 44] Future prospective studies will be important to determine which respiratory viruses lead to hospitalisations and lower peak lung function for those born preterm.

Limitations

Our data are limited by the parental reporting of hospitalisations, and therefore, our inability to identify the causative agent for the early-life respiratory admission. Further, we were unable to identify a precise age for each hospitalisation as the number of respiratory hospitalisations and an approximate age range was reported. A strength of this study was, however, that hospitalisation data were collected when participants were 5 years and 11 years of age, as well as at the current visit, ensuring a shorter time frame on recall. Regarding recall bias, we cannot exclude that those with current symptoms were not more likely to recall a previous respiratory admission. Similarly, confounding factors unaccounted for in this analysis could be related to both having a respiratory event during childhood and lower lung function in adult life. The greatest deficits in lung function following a respiratory admission were observed in those with BPD (figure 2). Our understanding of the associations between respiratory admission and later-life outcomes for the subgroup without BPD is limited due to the smaller size of this group (n=46 vs n=81) and the lower rate of respiratory hospitalisations (33% in those without-BPD vs 59% with-BPD). We were similarly limited in our ability to detect differences in other instances where the sample size was limited, for example, only three in the term-born control group reported a previous respiratory admission. Regardless, we provide important information on the potential role of early-life infections on lung health outcomes during adulthood.

The proportion of this cohort with BPD is higher than would be expected in a general population born 32 weeks gestation or less due to a deliberate recruitment strategy. It was anticipated that individuals with BPD would have the most complex and heterogeneous lung disease however, BPD (as defined once at 36 weeks corrected GA before the preterm infant has reached full term) is an imperfect predictor of long-term outcomes. We have, therefore, included both those with and without a BPD diagnosis in the analysis of risk factors for poorer outcomes. While those with and without BPD are representative of respective populations in the local area,[8] the reader should be aware that lung function deficits as described in the whole preterm cohort may be more severe than could be expected in a general population born ≤32 weeks due to this recruitment strategy.

Lastly, due to the large volume of the data presented and the intention to identify risk factors for lower peak lung function, longitudinal analysis was out of the scope of this manuscript. Future longitudinal analyses will complement these findings.

CONCLUSION

In conclusion, adolescence and young adulthood is supposed to be near the 'peak' of human lung health. However, survivors of preterm birth in the contemporary era commonly report respiratory symptoms, have structural lung damage and lower than expected lung function. As such, the evidence is mounting that many survivors are at increased risk of early-onset COPD and should be more closely monitored in the clinical setting and provided with anticipatory guidance on smoking, vaping and employment. Our study indicates that monitoring may be particularly important for those with an early-life readmission to hospital for a respiratory infection, however, it may not be until the fourth, fifth and sixth decades of life that the full impacts of early-life insults are fully realised.

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Contributors EFS and SJS wrote the original draft. EFS conducted the data analysis which was visualised and validated by NRH and SJS. GLH, ACW and SJS conceptualised the study, designed the methodology and acquired funding. EFS and NRH undertook project administration and investigation activities. ACW and CPM performed investigation activities relating to image analysis. All authors reviewed and edited the final manuscript. SJS is the guarantor and responsible for the overall content of this article.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the Child and Adolescent Health Service (CAHS) Human Research Ethics Committee (RGS0815). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Individual participant data that underlie the results reported in this article would be available after de-identification, assuming participant consent was given, along with the study protocol and analytic code, beginning 3 months after publication. Data would be made available to investigators providing a sound proposal that has been approved by an independent review committee to achieve the aims of the proposal. Proposals should be directed to shannon.simpson@telethonkids.org.au; to gain access, data requestors will need to sign a data access agreement.

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Title: Risk factors for respiratory morbidity in adolescents and young adults born preterm

Authors: Elizabeth F. Smith[1,2], Naomi R. Hemy[1], Graham L. Hall[1,2], Andrew C. Wilson[1,2,3], Conor P. Murray[3] and Shannon J. Simpson[1,2]

Online Data Supplement

Assessment of lung function (full details):

Assessment of lung function included spirometry, diffusing capacity for the lung, whole body plethysmography (Medisoft BodyBox 5500, Medisoft Corporation, Sorrines, Belgium); multiple breath washout (Exhalyzer D, Ecomedics, Duernten, Switzerland/EasyOne Pro Lab, NDD Medical Technologies, Zurich, Switzerland); fractional exhaled nitric oxide (HypAir FeNO, Medisoft Corporation, Sorrines, Belgium); and oscillometry (Tremoflo, Thorasys, Montreal, Canada). All lung function tests were performed according to ATS/ERS guidelines.[E1–6] The bronchodilator response was assessed by spirometry following the administration of 400mcg salbutamol via spacer, with a significant response defined as an improvement of ≥12% and 200ml in FEV_1 or FVC.[E7] Where possible, lung function outcomes were expressed as z-scores according to the Global Lung Function Initiative equations.[E8–10] Oscillometry outcomes were expressed as z-scores according to the reference equations published by Oostveen *et al,*[E11] with the exception of Rrs_{5-20}, expressed as an absolute difference. In adults, lung clearance index (LCI), moment ratio 1 and 2 (MR1, MR2) and specific airway conductance (sGaw), are independent of anthropometrics, and thus no adjustments have been made.[E12,13]

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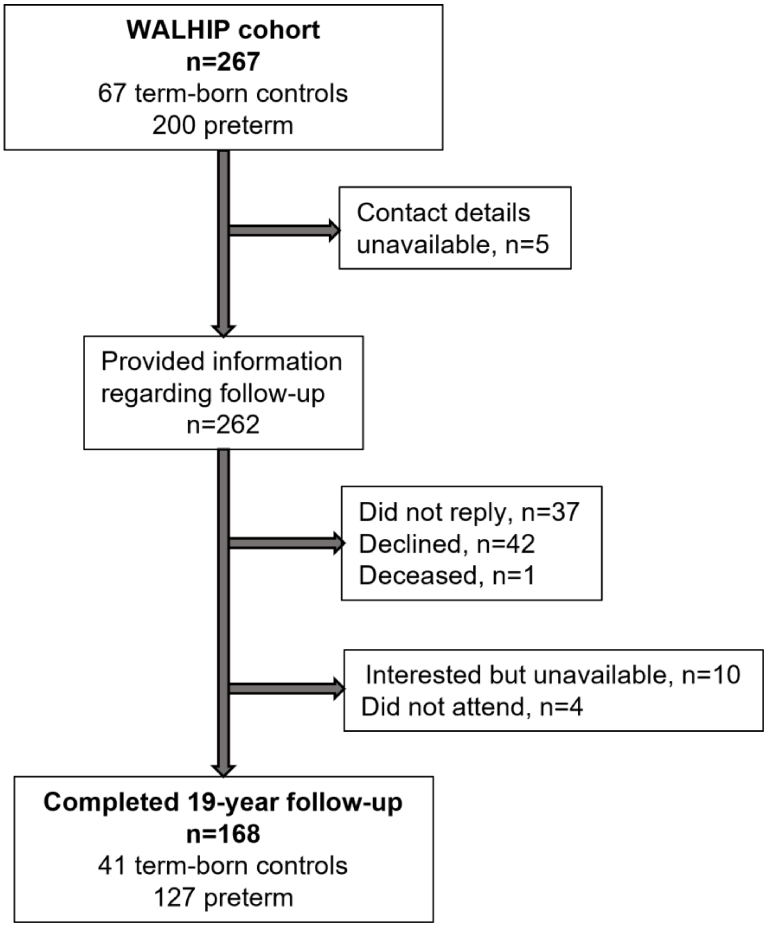

Figure E1. Flowchart describing recruitment of the WALHIP cohort at adolescent/young adulthood follow-up.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
Forced flows and volumes					
FEV_1 z-score					
Subpleural opacities	-0.187	**<0.001***	-0.287	-0.086	0.103
Hypoattenuation – Insp	0.168	0.218	-0.437	0.101	0.013
Hypoattenuation – Exp	-0.130	**0.007***	-0.224	-0.037	0.061
Peribronchial thickening	-0.226	**0.002***	-0.369	-0.082	0.076
Total CT score	-0.102	**<0.001***	-0.144	-0.060	0.163
FEV_1 z-score post-bronchodilator					
Subpleural opacities	-0.120	**0.013***	-0.215	-0.025	0.052
Hypoattenuation – Insp	-0.102	0.402	-0.341	0.138	0.006
Hypoattenuation – Exp	0.085	0.052	-0.172	0.001	0.033
Peribronchial thickening	-0.104	0.144	-0.244	0.036	0.019
Total CT score	-0.065	**0.002***	-0.106	-0.024	0.079
FVC z-score					
Subpleural opacities	-0.041	0.409	-0.139	0.057	0.006
Hypoattenuation – Insp	-0.016	0.896	-0.263	0.230	0.000
Hypoattenuation – Exp	-0.030	0.505	-0.1520	0.059	0.004
Peribronchial thickening	0.014	0.870	-0.155	0.183	0.000
Total CT score	-0.023	0.323	-0.069	0.023	0.009
FEV_1/FVC z-score					
Subpleural opacities	-0.184	**<0.001***	-0.286	-0.082	0.104
Hypoattenuation – Insp	-0.183	0.177	-0.451	0.084	0.017
Hypoattenuation – Exp	-0.116	**0.018***	-0.211	-0.020	0.050
Peribronchial thickening	-0.203	**0.028***	-0.384	-0.022	0.043
Total CT score	-0.104	**<0.001***	-0.150	-0.058	0.152
FEF_{25-75} z-score					
Subpleural opacities	-0.229	**<0.001***	-0.331	-0.126	0.152
Hypoattenuation – Insp	-0.194	0.165	-0.469	0.081	0.017
Hypoattenuation – Exp	-0.131	**0.009***	-0.229	-0.034	0.061
Peribronchial thickening	-0.195	**0.041***	-0.382	-0.009	0.038
Total CT score	-0.120	**<0.001***	-0.167	-0.073	0.192

Table E1.The relationship between spirometry outcomes and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
DLCO z-score					
Subpleural opacities	-0.106	**0.033***	-0.203	-0.008	0.037
Hypoattenuation – Insp	-0.288	**0.023***	-0.534	-0.041	0.043
Hypoattenuation – Exp	-0.041	0.363	-0.129	0.048	0.007
Peribronchial thickening	-0.040	0.572	-0.179	0.099	0.003
Total CT score	-0.048	**0.023***	-0.089	-0.007	0.043
KCO z-score					
Subpleural opacities	-0.180	**<0.001***	-0.268	-0.093	0.123
Hypoattenuation – Insp	-0.270	**0.023***	-0.502	-0.037	0.042
Hypoattenuation – Exp	0.026	0.537	-0.057	0.110	0.003
Peribronchial thickening	0.004	0.955	-0.127	0.135	0.000
Total CT score	-0.036	0.070	-0.075	0.003	0.027
VA z-score					
Subpleural opacities	0.087	0.108	-0.019	0.194	0.022
Hypoattenuation – Insp	-0.038	0.786	-0.311	0.236	0.001
Hypoattenuation – Exp	-0.086	0.075	-0.182	0.009	0.026
Peribronchial thickening	-0.053	0.489	-0.203	0.098	0.004
Total CT score	-0.017	0.468	-0.063	0.029	0.004

Table E2.The relationship between gas transfer (DLCO) outcomes and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
RV z-score					
Subpleural opacities	0.100	**0.005***	0.032	0.169	0.066
Hypoattenuation – Insp	0.017	0.856	-0.167	0.201	0.000
Hypoattenuation – Exp	-0.068	**0.037***	-0.131	-0.004	0.036
Peribronchial thickening	0.049	0.342	-0.052	0.149	0.008
Total CT score	0.007	0.630	-0.023	0.038	0.002
RV/TLC z-score					
Subpleural opacities	0.095	**0.022***	0.014	0.176	0.043
Hypoattenuation – Insp	0.014	0.899	-0.201	0.228	0.000
Hypoattenuation – Exp	-0.059	0.118	-0.134	0.015	0.020
Peribronchial thickening	0.052	0.383	-0.066	0.169	0.006
Total CT score	0.010	0.594	-0.026	0.045	0.002

Table E3.The relationship between residual volume and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
LCI					
Subpleural opacities	0.219	**0.004***	-0.073	0.364	0.065
Hypoattenuation – Insp	0.054	0.788	-0.345	0.453	0.001
Hypoattenuation – Exp	0.269	**<0.001***	0.158	0.381	0.153
Peribronchial thickening	0.428	**<0.001***	0.212	0.645	0.108
Total CT score	0.153	**<0.001***	0.093	0.212	0.170
MR1					
Subpleural opacities	0.060	**0.008***	0.016	0.103	0.055
Hypoattenuation – Insp	0.012	0.841	-0.107	0.131	0.000
Hypoattenuation – Exp	0.085	**<0.001***	0.053	0.118	0.173
Peribronchial thickening	0.114	**<0.001***	0.049	0.179	0.086
Total CT score	0.044	**<0.001***	0.027	0.062	0.161
MR2					
Subpleural opacities	0.523	**0.007***	0.145	0.901	0.056
Hypoattenuation – Insp	0.412	0.430	-0.617	1.441	0.005
Hypoattenuation – Exp	0.694	**<0.001***	0.406	0.982	0.152
Peribronchial thickening	1.269	**<0.001***	0.721	1.818	0.142
Total CT score	0.404	**<0.001***	0.252	0.557	0.178

Table E4.The relationship between ventilation heterogeneity and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
FeNO					
Subpleural opacities	-0.972	0.343	-2.991	1.048	0.007
Hypoattenuation – Insp	1.007	0.704	-4.224	6.238	0.001
Hypoattenuation – Exp	-0.486	0.602	-2.328	1.356	0.002
Peribronchial thickening	4.102	**0.004***	1.313	6.891	0.065
Total CT score	0.162	0.715	-0.714	1.038	0.001

Table E5. The relationship between fractional exhaled nitric oxide (FeNO) and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
Rrs_5 z-score					
Subpleural opacities	0.006	0.891	-0.081	0.093	0.000
Hypoattenuation – Insp	0.136	0.227	-0.086	0.359	0.012
Hypoattenuation – Exp	0.021	0.591	-0.057	0.100	0.002
Peribronchial thickening	0.029	0.639	-0.094	0.152	0.002
Total CT score	0.021	0.270	-0.013	0.058	0.010
Fres z-score					
Subpleural opacities	0.064	0.155	-0.025	0.154	0.017
Hypoattenuation – Insp	0.001	0.993	-0.232	0.234	0.000
Hypoattenuation – Exp	0.033	0.429	-0.049	0.115	0.005
Peribronchial thickening	0.039	0.552	-0.089	0.167	0.003
Total CT score	0.030	0.129	-0.009	0.068	0.019
AX z-score					
Subpleural opacities	0.039	0.346	-0.042	0.119	0.007
Hypoattenuation – Insp	0.036	0.735	-0.173	0.245	0.001
Hypoattenuation – Exp	0.032	0.392	-0.042	0.105	0.006
Peribronchial thickening	0.019	0.748	-0.097	0.134	0.001
Total CT score	0.024	0.167	-0.010	0.059	0.016
Xrs_5 z-score					
Subpleural opacities	0.026	0.537	-0.057	0.108	0.003
Hypoattenuation – Insp	0.075	0.486	-0.138	0.288	0.004
Hypoattenuation – Exp	0.038	0.319	-0.037	0.113	0.008
Peribronchial thickening	0.003	0.962	-0.115	0.120	0.000
Total CT score	0.025	0.173	-0.011	0.060	0.015

Table E6. The relationship between airway mechanics (oscillometry) and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Univariate Analysis				
	B	p-value	95% CI Lower	95% CI Upper	R^2
sGaw					
Subpleural opacities	-0.009	**0.016***	-0.016	-0.002	0.050
Hypoattenuation – Insp	-0.010	0.267	-0.028	0.008	0.011
Hypoattenuation – Exp	-0.006	0.062	-0.013	0.000	0.030
Peribronchial thickening	-0.018	**<0.001***	-0.027	-0.008	0.097
Total CT score	-0.005	**<0.001***	-0.008	-0.002	0.092

Table E7. The relationship between airway mechanics (plethysmography) and structural abnormalities on chest CT in those born preterm. *p<0.05.

	Wheeze		**Wheeze during exercise**		**Cough**		**Rattle**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Number, N (%)	112 (88.2%)	15 (11.8%)	104 (81.9)	23 (18.1%)	63 (49.6%)	64 (50.4%)	106 (83.5%)	21 (16.5%)
R5-20	0.384 (0.613)	**1.391 (1.404)***	0.410 (0.704)	**0.924 (1.107)***	0.403 (0.680)	0.605 (0.920)	0.409 (0.672)	**0.978 (1.220)***
R5 z-score	1.234 (1.161)	**2.002 (1.103)***	1.190 (1.146)	**1.931 (1.143)***	1.178 (1.338)	1.472 (0.982)	1.239 (1.177)	1.755 (1.105)
Fres z-score	1.839 (1.431)	2.452 (1.254)	1.807 (1.401)	2.374 (1.462)	1.721 (1.522)	2.091 (1.297)	1.830 (1.439)	2.311 (1.279)
AX z-score	1.812 (1.097)	**2.731 (1.262)***	1.821 (1.103)	**2.369 (1.280)***	1.693 (1.171)	**2.148 (1.097)***	1.820 (1.099)	**2.428 (1.300)***
X5 z-score	1.135 (1.141)	**2.998 (2.482)***	1.245 (1.385)	1.864 (1.820)	1.034 (1.418)	**1.679 (1.494)***	1.168 (1.180)	**2.301 (2.324)***
FEV_1 z-score	-0.73 (1.06)	**-1.96 (1.29)***	-0.80 (1.13)	-1.21 (1.27)	-0.73 (1.27)	-1.03 (1.03)	-0.76 (1.07)	**-1.46 (1.43)***
FEV_1 z-score post-bronchodilator	-0.17 (0.98)	**-1.09 (0.99)***	-0.21 (0.99)	-0.53 (1.13)	-0.22 (1.16)	-0.33 (0.86)	-0.20 (0.99)	-0.64 (1.13)
FVC z-score	0.04 (1.02)	-0.47 (0.98)	0.01 (1.01)	0.00 (1.12)	0.07 (1.09)	-0.10 (0.95)	-0.04 (1.02)	-0.29 (1.05)
FEV_1/FVC z-score	-1.09 (1.11)	**-1.81 (1.05)***	-1.07 (1.14)	**-1.61 (0.90)***	-1.14 (1.19)	-1.20 (1.05)	-1.12 (1.14)	-1.47 (0.95)
FEF_{25-75} z-score	-1.18 (1.11)	**-2.22 (1.15)***	-1.17 (1.16)	**-1.82 (1.00)***	-1.24 (1.27)	-1.36 (1.02)	-1.22 (1.15)	-1.74 (1.13)
FEF_{75} z-score	-0.81 (1.03)	**-1.69 (1.15)***	-0.81 (1.07)	**-1.34 (0.99)***	-0.88 (1.15)	-0.94 (0.98)	-0.82 (1.05)	**-1.39 (1.09)***
DLCO z-score	0.87 (1.11)	0.76 (0.83)	0.90 (1.09)	0.64 (1.03)	1.01 (1.14)	0.70 (1.01)	0.93 (1.09)	0.44 (0.97)
VA z-score	0.71 (1.17)	0.11 (1.19)	0.70 (1.17)	0.37 (1.24)	0.82 (1.21)	0.47 (1.13)	0.79 (1.18)	**-0.14 (0.87)***
KCO z-score	0.29 (0.98)	0.68 (1.20)	0.34 (0.98)	0.33 (1.16)	0.35 (1.02)	0.32 (1.02)	0.29 (0.99)	0.55 (1.11)
TLC z-score	0.30 (0.82)	0.17 (0.87)	0.30 (0.82)	0.19 (0.84)	0.40 (0.85)	0.17 (0.78)	0.35 (0.82)	**-0.06 (0.74)***
FRC z-score	0.53 (0.89)	0.71 (1.10)	0.55 (0.92)	0.54 (0.92)	0.57 (0.86)	0.52 (0.98)	0.57 (0.85)	0.43 (1.21)
RV z-score	0.65 (0.77)	0.93 (0.96)	0.68 (0.81)	0.70 (0.72)	0.68 (0.83)	0.70 (0.76)	0.69 (0.75)	0.67 (1.01)
RV/TLC z-score	0.72 (0.90)	1.13 (1.07)	0.76 (0.94)	0.82 (0.88)	0.71 (0.96)	0.83 (0.90)	0.75 (0.89)	0.88 (1.11)
Median (IQR)								
FeNO (ppb)	15 (10,24)	17 (14, 45)	15 (10, 26)	16 (10, 23)	15 (11,27)	16 (10, 23)	15 (10, 26)	16 (13, 19)
sGAW	0.16 (0.12, 0.23)	**0.11 (0.05, 0.14)**	0.16 (0.12, 0.23)	**0.12 (0.10, 0.15)**	0.16 (0.11, 0.24)	0.15 (0.11, 0.20)	0.15 (0.12, 0.23)	0.14 (0.08, 0.20)
LCI	7.45 (6.88, 8.22)	7.88 (7.27, 9.99)	7.60 (6.88, 8.22)	7.48 (7.02, 9.32)	7.44 (6.78, 8.42)	7.64 (6.96, 8.22)	7.44 6.88, 8.03)	**8.20 (7.20, 10.15)**
Moment Ratio 1	1.96 (1.67, 2.15)	2.01 (1.72, 2.38)	1.99 (1.72, 2.19)	1.93 (1.64, 2.18)	2.06 (1.68, 2.17)	1.94 (1.63, 2.28)	1.94 (1.65, 2.15)	2.26 (1.80, 2.57)
Moment Ratio 2	7.03 (5.45, 8.85)	7.58 (6.17, 11.00)	7.18 (5.61, 9.57)	6.92 (5.26, 10.27)	7.56 (5.37, 9.84)	6.96 (5.61, 9.80)	6.98 (5.36, 8.74)	9.69 (6.66, 11.72)

Table E8. The relationship between lung function and respiratory symptoms. Data expressed as mean (SD), unless otherwise indicated. *p<0.05 compared to no [symptom] group.

	Wheeze		**Wheeze during exercise**		**Cough**		**Rattle**	
	No (n=110)	**Yes (n=15)**	**No (n=102)**	**Yes (n=23)**	**No (n=62)**	**Yes (n=63)**	**No (n=105)**	**Yes (n=20)**
Linear/triangular subpleural opacities								
Presence, n participants (%)	74 (67.3%)	10 (66.7%)	67 (65.7%)	17 (73.9%)	40 (64.5%)	44 (69.8%)	71 (67.6%)	13 (65.0%)
Extent (CT score) (IQR)	2 (0,4)	2 (0,3)	2 (0,4)	2 (0,3)	2 (0,3)	2 (0,4)	2 (0,4)	2 (0,3)
Decreased pulmonary attenuation—inspiration								
Presence	12 (10.9%)	2 (13.3%)	12 (11.8%)	2 (8.7%)	5 (8.1%)	9 (14.3%)	11 (10.5%)	3 (15.0%)
Extent	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Decreased pulmonary attenuation—expiration								
Presence	74 (67.3%)	12 (80.0%)	68 (66.7%)	18 (78.3%)	41 (66.1%)	45 (71.4%)	69 (65.7%)	17 (85.0%)
Extent	2 (0,4)	2 (1,5)	2 (0,4)	2 (1,4)	2 (0,4)	2 (0,5)	2 (0,4)	4 (1,6)
Decreased bronchial: arterial ratio								
Presence	3 (2.7%)	0 (0%)	3 (2.9%)	0 (0%)	3 (4.8%)	0 (0%)	3 (2.9%)	0 (0%)
Extent	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Bronchiectasis								
Presence	4 (3.6%)	1 (6.7%)	5 (4.9%)	0 (0%)	3 (4.8%)	2 (3.2%)	4 (3.8%)	1 (5.0%)
Extent	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Bronchial wall thickening								
Presence	11 (10.0%)	**7 (46.7%)***	12 (11.8%)	6 (26.1%)	6 (9.7%)	12 (19.0%)	11 (10.5%)	**7 (35.0%)***
Extent	0 (0,0)	**0 (0,5)***	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	**0 (0,3)***
Bullae								
Presence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Extent	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Emphysema								
Presence	3 (2.7%)	1 (6.7%)	4 (3.9%)	0 (0%)	1 (1.6%)	3 (4.8%)	3 (2.9%)	1 (5.0%)
Extent	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Collapse/consolidation								
Presence	7 (6.4%)	2 (13.3%)	7 (6.9%)	2 (8.7%)	1 (1.6%)	**8 (12.7%)***	5 (4.8%)	**4 (20.0%)***
Extent	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	**0 (0,0)***	0 (0,0)	**0 (0,0)***
Structural abnormalities on chest CT								
Presence, n participants (%)	95 (86.4%)	15 (100%)	87 (85.3%)	23 (100%)	52 (83.9%)	54 (92.1%)	91 (86.7%)	19 (95.0%)
Total CT score	4 (1,8)	5 (2,10)	4 (1,8)	5 (2,8)	4 (1,8)	5 (2,8)	4 (1,8)	6 (3,11)

Table E9. The relationship between lung structure abnormalities and respiratory symptoms. Data expressed as n (%) and median (IQR). *p<0.05 compared to no [symptom] group.

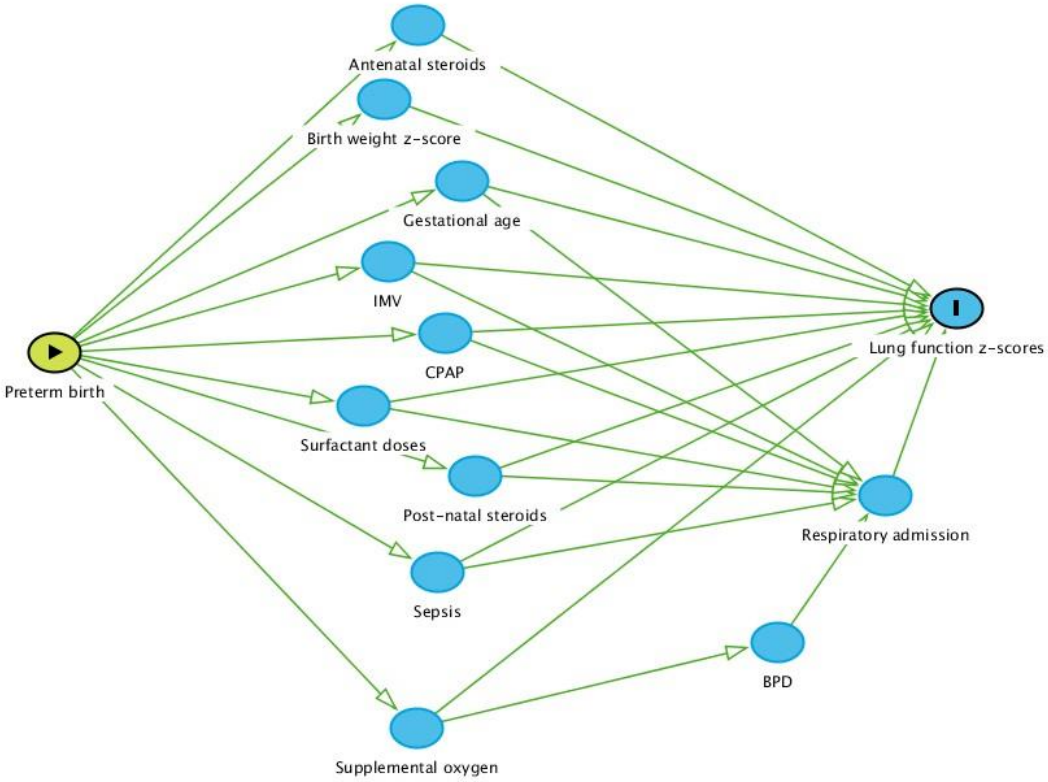

Figure E2. Direct acyclic graph for relationships between Post-natal/early life factors and lung function in children born preterm. Lung function outcomes are the outcome variable in blue and preterm birth the exposure variable (green)). Arrows in green denote causal paths.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
FEV_1 z-score									R^2=0.101; p=0.148
Antenatal Steroids (y/n)	-0.006	0.316	-0.18	0.006					
Birth weight z-score	0.265	**0.029***	0.028	0.503					
Gestation Age (w)	0.098	**0.024***	0.013	0.183	-0.022	0.797	-0.189	0.145	0.048
IMV (d)	-0.014	**0.006***	-0.025	-0.004	-0.005	0.655	-0.026	0.017	0.014
Supplementary O2 (d)	-0.007	**0.002***	-0.011	-0.003	-0.005	0.296	-0.014	0.004	0.016
CPAP (d)	-0.009	0.267	-0.024	0.007	-0.001	0.919	-0.022	0.020	0.000
Surfactant doses (n)	-0.087	0.476	-0.327	0.154	0.069	0.608	-0.197	0.335	0.002
Post-natal steroids (y/n)	-0.418	0.078	-0.884	0.048	-0.034	0.910	-0.627	0.559	0.000
Sepsis (n)	-0.364	0.108	-0.810	0.081	-0.182	0.470	-0.681	0.316	0.003
Respiratory admission (y/n)	-0.435	**0.039***	-0.848	-0.022	-0.320	0.142	-0.749	0.109	0.018
FEV_1 z-score post-bronchodilator									R^2=0.062; p=0.222
Antenatal Steroids (y/n)	-0.007	0.200	-0.017	-0.004					
Birth weight z-score	0.262	0.018	0.045	0.479					
Gestation Age (w)	0.064	0.104	-0.013	0.141	0.000	0.998	-0.152	0.152	0.027
IMV (d)	-0.008	0.128	-0.017	0.002	0.005	0.611	-0.015	0.025	0.000
Supplementary O2 (d)	-0.005	**0.014***	-0.008	-0.001	-0.006	0.136	-0.014	0.002	0.024
CPAP (d)	-0.009	0.222	-0.022	0.005	0.000	0.990	-0.020	0.020	0.000
Surfactant doses (n)	-0.004	0.974	-0.217	0.210	0.113	0.355	-0.128	0.354	0.007
Post-natal steroids (y/n)	-0.223	0.304	-0.651	0.205	-0.032	0.908	-0.577	0.513	0.000
Sepsis (n)	-0.247	0.223	-0.646	0.152	-0.127	0.579	-0.579	0.325	0.002
Respiratory admission (y/n)	-0.166	0.380	-0.539	0.207	-0.071	0.719	-0.464	0.321	0.001
FVC z-score									R^2=0.072; p=0.444
Antenatal Steroids (y/n)	-0.006	0.319	-0.018	0.006					
Birth weight z-score	0.221	0.050	0.000	0.441					
Gestation Age (w)	0.048	0.223	-0.030	0.126	-0.036	0.645	-0.192	0.119	0.017
IMV (d)	-0.008	0.130	-0.017	0.002	-0.006	0.575	-0.028	0.016	0.003
Supplementary O2 (d)	-0.004	0.062	-0.007	0.000	-0.003	0.568	-0.011	0.006	0.008
CPAP (d)	-0.011	0.100	-0.025	0.002	-0.014	0.183	-0.035	0.007	0.015
Surfactant doses (n)	0.060	0.586	-0.157	0.276	0.193	0.121	-0.052	0.437	0.020
Post-natal steroids (y/n)	-0.235	0.289	-0.671	0.202	-0.104	0.714	-0.662	0.455	0.002
Sepsis (n)	-0.161	0.442	-0.576	0.253	-0.007	0.975	-0.473	0.458	0.000
Respiratory admission (y/n)	0.100	0.606	-0.283	0.483	0.183	0.372	-0.222	0.589	0.007
FEV_1/FVC z-score									R^2=0.113; p=0.126
Antenatal Steroids (y/n)	-0.009	0.187	-0.022	0.004					
Birth weight z-score	0.115	0.355	-0.130	0.359					
Gestation Age (w)	0.051	0.242	-0.035	0.136	0.018	0.833	-0.149	0.185	0.015
IMV (d)	-0.006	0.277	-0.017	0.005	0.012	0.295	-0.011	0.036	0.000
Supplementary O2 (d)	-0.004	0.079	-0.008	0.000	-0.005	0.283	-0.015	0.004	0.013
CPAP (d)	0.000	0.951	-0.015	0.016	0.014	0.220	-0.008	0.036	0.018
Surfactant doses (n)	-0.143	0.232	-0.378	0.093	-0.106	0.426	-0.369	0.157	0.006
Post-natal steroids (y/n)	-0.264	0.276	-0.741	0.213	-0.169	0.577	-0.769	0.431	0.001
Sepsis (n)	-0.214	0.354	-0.670	0.242	-0.265	0.295	-0.766	0.235	0.004
Respiratory admission (y/n)	-0.613	**0.003***	-1.016	-0.210	-0.561	**0.012***	-0.998	-0.125	0.057

FEF_{25-75} z-score									R^2=0.125; p=0.082
Antenatal Steroids (y/n)	-0.011	0.095	-0.025	0.002					
Birth weight z-score	0.277	**0.029***	0.029	0.525					
Gestation Age (w)	0.076	0.088	-0.012	0.164	-0.016	0.852	-0.186	0.154	0.032
IMV (d)	-0.011	0.058	-0.022	0.000	0.007	0.555	-0.017	0.031	0.004
Supplementary O2 (d)	-0.006	**0.007***	-0.010	-0.002	-0.007	0.146	-0.017	0.003	0.027
CPAP (d)	-0.004	0.585	-0.020	0.011	0.009	0.447	-0.014	0.032	0.007
Surfactant doses (n)	-0.127	0.302	-0.371	0.116	-0.030	0.823	-0.298	0.237	0.001
Post-natal steroids (y/n)	-0.320	0.200	-0.811	0.171	-0.088	0.775	-0.699	0.523	0.000
Sepsis (n)	-0.316	0.181	-0.781	0.149	-0.289	0.263	-0.798	0.220	0.005
Respiratory admission (y/n)	-0.629	**0.003***	-1.045	-0.213	-0.535	**0.019***	-0.979	-0.090	0.049

Table E10. Neonatal factors influencing forced flows and volumes in preterm adolescents and young adults. *p<0.05.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
DLCO z-score									R^2=0.054; p=0.604
Antenatal Steroids (y/n)	-0.012	0.065	-0.025	0.001					
Birth weight z-score	0.172	0.115	-0.042	0.386					
Gestation Age (w)	0.045	0.262	-0.034	0.124	-0.032	0.689	-0.193	0.128	0.012
IMV (d)	-0.008	0.129	-0.017	0.002	-0.003	0.793	-0.023	0.017	0.006
Supplementary O2 (d)	-0.004	0.068	-0.008	0.000	-0.005	0.225	-0.013	0.003	0.010
CPAP (d)	-0.004	0.618	-0.018	0.011	-0.003	0.779	-0.023	0.018	0.000
Surfactant doses (n)	-0.056	0.617	-0.275	0.164	0.006	0.962	-0.247	0.259	0.000
Post-natal steroids (y/n)	-0.274	0.219	-0.714	0.165	-0.063	0.829	-0.638	0.512	0.001
Sepsis (n)	0.196	0.356	-0.223	0.616	0.411	0.090	-0.066	0.887	0.024
Respiratory admission (y/n)	-0.037	0.849	-0.425	0.351	0.079	0.704	-0.332	0.489	0.001
KCO z-score									R^2=0.117; p=0.073
Antenatal Steroids (y/n)	-0.004	0.464	-0.016	0.534					
Birth weight z-score	0.079	0.442	-0.123	0.280					
Gestation Age (w)	0.033	0.382	-0.041	0.106	-0.098	0.182	-0.243	0.047	0.006
IMV (d)	-0.009	0.052	-0.018	0.000	-0.005	0.549	-0.024	0.013	0.035
Supplementary O2 (d)	-0.003	0.066	-0.007	0.000	-0.005	0.177	-0.013	0.002	0.015
CPAP (d)	0.003	0.700	-0.011	0.016	0.005	0.590	-0.014	0.024	0.002
Surfactant doses (n)	-0.287	**0.005***	-0.485	-0.088	-0.295	**0.012***	-0.523	-0.066	0.047
Post-natal steroids (y/n)	-0.300	0.150	-0.710	0.110	-0.009	0.973	-0.528	0.510	0.000
Sepsis (n)	0.072	0.717	-0.321	0.466	0.274	0.209	-0.156	0.704	0.013
Respiratory admission (y/n)	-0.061	0.740	-0.423	0.302	-0.022	0.905	-0.393	0.348	0.000
VA z-score									R^2=0.089; p=0.222
Antenatal Steroids (y/n)	-0.010	0.148	-0.024	0.004					
Birth weight z-score	0.115	0.336	-0.120	0.349					
Gestation Age (w)	0.017	0.700	-0.069	0.103	0.081	0.348	-0.089	0.251	0.002
IMV (d)	0.002	0.700	-0.009	0.013	0.004	0.686	-0.017	0.026	0.015
Supplementary O2 (d)	0.000	0.854	-0.005	0.004	0.000	0.945	-0.009	0.008	0.000
CPAP (d)	-0.009	0.255	-0.024	0.006	-0.011	0.334	-0.032	0.011	0.002
Surfactant doses (n)	0.282	**0.018***	0.048	0.516	0.371	**0.007***	0.103	0.639	0.063
Post-natal steroids (y/n)	0.049	0.841	-0.433	0.531	-0.053	0.864	-0.662	0.557	0.000
Sepsis (n)	0.138	0.549	-0.317	0.592	0.161	0.528	-0.344	0.666	0.003
Respiratory admission (y/n)	0.025	0.907	-0.398	0.448	0.126	0.569	-0.310	0.561	0.003

Table E11. Neonatal factors influencing gas transfer in preterm adolescents and young adults. *p<0.05.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
RV z-score									**R^2=0.133; p=0.037**
Antenatal Steroids (y/n)	-0.001	0.842	-0.009	0.007					
Birth weight z-score	-0.174	**0.029***	-0.330	-0.019					
Gestation Age (w)	-0.051	0.075	-0.108	0.005	0.105	0.067	-0.007	0.217	0.028
IMV (d)	0.012	**<0.001***	0.005	0.019	0.016	**0.026***	0.002	0.030	0.066
Supplementary O2 (d)	0.004	**0.003***	0.001	0.007	0.002	0.506	-0.004	0.008	0.011
CPAP (d)	0.006	0.244	-0.004	0.016	0.008	0.263	-0.006	0.023	0.016
Surfactant doses (n)	0.190	**0.019***	0.031	0.348	0.105	0.249	-0.075	0.285	0.010
Post-natal steroids (y/n)	0.293	0.066	-0.020	0.607	-0.076	0.706	-0.477	0.324	0.001
Sepsis (n)	0.223	0.149	-0.081	0.528	0.007	0.968	-0.326	0.340	0.000
Respiratory admission (y/n)	-0.010	0.946	-0.294	0.275	-0.051	0.727	-0.340	0.238	0.001
RV/TLC z-score									**R^2=0.146; p=0.020**
Antenatal Steroids (y/n)	0.001	0.904	-0.009	0.010					
Birth weight z-score	-0.281	**0.002***	-0.460	-0.103					
Gestation Age (w)	-0.065	0.054	-0.131	0.001	0.132	**0.045***	0.003	0.262	0.035
IMV (d)	0.014	**<0.001***	0.006	0.022	0.019	**0.024***	0.002	0.035	0.059
Supplementary O2 (d)	0.005	**0.001***	0.002	0.009	0.003	0.401	-0.004	0.010	0.018
CPAP (d)	0.011	0.076	-0.001	0.023	0.015	0.081	-0.002	0.031	0.030
Surfactant doses (n)	0.180	0.059	-0.007	0.367	0.048	0.647	-0.159	0.255	0.002
Post-natal steroids (y/n)	0.385	**0.039***	0.021	0.751	-0.024	0.918	-0.486	0.438	0.000
Sepsis (n)	0.290	0.106	-0.063	0.643	0.014	0.944	-0.370	0.398	0.000
Respiratory admission (y/n)	-0.022	0.895	-0.355	0.310	-0.089	0.598	-0.423	0.245	0.002

Table E12. Neonatal factors influencing residual volume in preterm adolescents and young adults. *p<0.05.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
Rrs5 z-score									R^2=0.091; p=0.192
Antenatal Steroids (y/n)	0.007	0.272	-0.005	0.019					
Birth weight z-score	0.093	0.431	-0.141	0.327					
Gestation Age (w)	-0.080	0.063	-0.164	0.004	-0.166	0.054	-0.335	0.003	0.029
IMV (d)	0.002	0.691	-0.008	0.013	-0.009	0.405	-0.030	0.012	0.014
Supplementary O2 (d)	0.003	0.171	-0.001	0.007	0.004	0.339	-0.005	0.013	0.001
CPAP (d)	0.006	0.425	-0.009	0.021	-0.010	0.354	-0.032	0.011	0.008
Surfactant doses (n)	-0.066	0.582	-0.303	0.171	-0.148	0.279	-0.418	0.121	0.014
Post-natal steroids (y/n)	-0.258	0.276	-0.726	0.209	-0.520	0.092	-1.127	0.087	0.022
Sepsis (n)	-0.036	0.876	-0.490	0.418	-0.149	0.560	-0.653	0.355	0.003
Respiratory admission (y/n)	0.134	0.526	-0.283	0.552	-0.037	0.868	-0.471	0.398	0.000
Fres z-score									**R^2=0.133; p=0.037**
Antenatal Steroids (y/n)	0.007	0.337	-0.007	0.022					
Birth weight z-score	-0.197	0.169	-0.479	0.085					
Gestation Age (w)	-0.156	**0.002***	-0.256	-0.057	-0.178	0.079	-0.376	0.021	0.078
IMV (d)	0.012	0.056	0.000	0.024	-0.013	0.303	-0.038	0.012	0.003
Supplementary O2 (d)	0.008	**0.002***	0.003	0.013	0.008	0.127	-0.002	0.018	0.013
CPAP (d)	0.012	0.183	-0.006	0.031	-0.014	0.267	-0.040	0.011	0.010
Surfactant doses (n)	-0.002	0.989	-0.292	0.288	-0.223	0.171	-0.544	0.098	0.016
Post-natal steroids (y/n)	0.159	0.582	-0.410	0.728	-0.288	0.427	-1.004	0.428	0.006
Sepsis (n)	0.429	0.121	-0.114	0.973	0.235	0.436	-0.359	0.828	0.004
Respiratory admission (y/n)	0.403	0.116	-0.101	0.908	0.182	0.488	-0.336	0.699	0.004
AX z-score									R^2=0.117; p=0.068
Antenatal Steroids (y/n)	0.003	0.635	-0.009	0.015					
Birth weight z-score	-0.135	0.245	-0.363	0.094					
Gestation Age (w)	-0.106	0.011	-0.187	-0.025	-0.126	0.128	-0.288	0.037	0.054
IMV (d)	0.008	0.125	-0.002	0.018	-0.009	0.396	-0.029	0.012	0.003
Supplementary O2 (d)	0.005	**0.009***	0.001	0.009	0.006	0.148	-0.002	0.015	0.010
CPAP (d)	0.007	0.336	-0.008	0.022	-0.012	0.256	-0.033	0.009	0.012
Surfactant doses (n)	-0.031	0.792	-0.264	0.201	-0.175	0.185	-0.435	0.085	0.017
Post-natal steroids (y/n)	0.027	0.908	-0.433	0.487	-0.321	0.280	-0.906	0.264	0.010
Sepsis (n)	0.228	0.308	-0.214	0.670	0.114	0.644	-0.372	0.600	0.001
Respiratory admission (y/n)	0.401	0.051	-0.002	0.804	0.247	0.246	-.0172	0.666	0.011
Xrs5 z-score									R^2=0.107; p=0.105
Antenatal Steroids (y/n)	-0.002	0.817	-0.017	0.013					
Birth weight z-score	-0.120	0.424	-0.415	0.176					
Gestation Age (w)	-0.121	**0.025***	-0.226	-0.016	-0.076	0.479	-0.287	0.136	0.042
IMV (d)	0.011	0.090	-0.002	0.024	-0.004	0.746	-0.031	0.022	0.000
Supplementary O2 (d)	0.007	**0.007***	0.002	0.012	0.010	0.084	-0.001	0.021	0.018
CPAP (d)	0.008	0.393	-0.011	0.028	-0.013	0.337	-0.040	0.014	0.008
Surfactant doses (n)	0.011	0.940	-0.289	0.312	-0.151	0.378	-0.488	0.187	0.009
Post-natal steroids (y/n)	-0.028	0.926	-0.622	0.566	-0.583	0.131	-1.343	0.177	0.019
Sepsis (n)	0.268	0.354	-0.303	0.839	0.083	0.796	-0.549	0.714	0.000
Respiratory admission (y/n)	0.505	0.057	-0.016	1.025	0.317	0.252	-0.228	0.861	0.010

Table E13. Neonatal factors influencing airway mechanics (oscillometry) in preterm adolescents and young adults. *p<0.05.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
Specific Airway Conductance (sGaw)									R^2=0.076; p=0.367
Antenatal Steroids (y/n)	0.000	0.631	-0.001	0.001					
Birth weight z-score	0.005	0.538	-0.011	0.021					
Gestation Age (w)	0.004	0.149	-0.002	0.010	0.002	0.747	-0.010	0.013	0.021
IMV (d)	-0.001	0.084	-0.001	0.000	0.000	0.916	-0.001	0.002	0.007
Supplementary O2 (d)	0.000	0.058	-0.001	0.000	0.000	0.345	-0.001	0.000	0.004
CPAP (d)	0.000	0.615	-0.001	0.001	0.001	0.212	-0.001	0.002	0.019
Surfactant doses (n)	-0.007	0.374	-0.023	0.009	-0.004	0.675	-0.023	0.015	0.001
Post-natal steroids (y/n)	-0.017	0.290	-0.049	0.015	0.005	0.817	-0.037	0.047	0.001
Sepsis (n)	0.000	0.982	-0.031	0.030	0.004	0.805	-0.030	0.039	0.002
Respiratory admission (y/n)	-0.032	**0.024**	-0.060	-0.004	-0.024	0.111	-0.054	0.006	0.022

Table E14. Neonatal factors influencing airway mechanics (plethysmography) in preterm adolescents and young adults. *p<0.05.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
Fractional Exhaled Nitric Oxide (FeNO)									**R^2=0.140; p=0.024**
Antenatal Steroids (y/n)	-0.070	0.547	-0.300	0.160					
Birth weight z-score	2.663	0.237	-1.775	7.101					
Gestation Age (w)	2.280	**0.005***	0.712	3.849	1.353	0.393	-1.771	4.476	0.066
IMV (d)	-0.270	**0.006***	-0.462	-0.077	0.097	0.624	-0.294	0.489	0.007
Supplementary O2 (d)	-0.126	**0.001**	-0.202	-0.049	-0.111	0.178	-0.273	0.051	0.009
CPAP (d)	-0.123	0.403	-0.413	0.167	0.251	0.217	-0.150	0.652	0.005
Surfactant doses (n)	-6.647	**0.003***	-11.009	-2.284	-4.344	0.087	-9.335	0.646	0.027
Post-natal steroids (y/n)	-8.470	0.060	-17.288	0.347	0.317	0.956	-10.921	11.555	0.000
Sepsis (n)	-7.319	0.092	-15.852	1.214	-1.280	0.786	-10.611	8.052	0.002
Respiratory admission (y/n)	4.171	0.300	-3.756	12.098	7.383	0.072	-0.666	15.431	0.025

Table E15. Neonatal factors influencing airway inflammation (fractional exhaled nitric oxide (FeNO) in preterm adolescents and young adults. *p<0.05.

	Univariate Analysis				Multivariable Linear Regression Analysis				
	B	p-value	95% CI Lower	95% CI Upper	B	p-value	95% CI Lower	95% CI Upper	Model R^2 change
Lung Clearance Index (LCI)									R^2=0.065; p=0.647
Antenatal Steroids (y/n)	-0.004	0.806	-0.037	0.029					
Birth weight z-score	-0.314	0.106	-0.696	0.068					
Gestation Age (w)	-0.083	0.215	-0.216	0.049	-0.074	0.572	-0.334	0.186	0.016
IMV (d)	0.013	0.173	-0.00	0.032	0.000	0.996	-0.042	0.042	0.006
Supplementary O2 (d)	0.004	0.311	-0.003	0.011	-0.001	0.904	-0.018	0.016	0.002
CPAP (d)	0.001	0.946	-0.022	0.024	-0.013	0.504	-0.050	0.025	0.002
Surfactant doses (n)	0.116	0.514	-0.236	0.468	0.012	0.952	-0.391	0.416	0.000
Post-natal steroids (y/n)	0.232	0.575	-0.588	1.053	0.030	0.953	-0.977	1.038	0.000
Sepsis (n)	0.785	**0.031***	0.075	1.495	0.802	0.063	-0.061	1.665	0.035
Respiratory admission (y/n)	0.312	0.259	-0.232	0.855	0.218	0.529	-0.468	0.905	0.004
Moment Ratio 1 (MR1)									R^2=0.069; p=0.597
Antenatal Steroids (y/n)	-0.004	0.426	-0.014	0.006					
Birth weight z-score	-0.049	0.392	-0.164	0.065					
Gestation Age (w)	-0.025	0.205	-0.065	0.014	-0.037	0.340	-0.114	0.040	0.017
IMV (d)	0.005	0.107	-0.001	0.010	0.001	0.831	-0.011	0.014	0.011
Supplementary O2 (d)	0.001	0.444	-0.001	0.003	-0.001	0.552	-0.006	0.003	0.013
CPAP (d)	0.001	0.757	-0.008	0.006	-0.004	0.473	-0.015	0.007	0.002
Surfactant doses (n)	0.032	0.549	-0.073	0.136	0.003	0.961	-0.122	0.116	0.000
Post-natal steroids (y/n)	0.155	0.206	-0.087	0.396	0.085	0.574	-0.213	0.383	0.002
Sepsis (n)	0.203	0.059	-0.008	0.415	0.192	0.139	-0.064	0.447	0.024
Respiratory admission (y/n)	0.041	0.619	-0.121	0.202	0.004	0.968	-0.199	0.207	0.000
Moment Ratio 2 (MR2)									R^2=0.060; p=0.699
Antenatal Steroids (y/n)	-0.027	0.534	-0.113	0.059					
Birth weight z-score	-0.564	0.268	-1.570	0.442					
Gestation Age (w)	-0.203	0.248	-0.550	0.144	-0.262	0.448	-0.943	0.420	0.014
IMV (d)	0.037	0.136	-0.012	0.086	0.014	0.798	-0.096	0.124	0.010
Supplementary O2 (d)	0.007	0.459	-0.012	0.026	-0.011	0.605	-0.055	0.032	0.009
CPAP (d)	-0.010	0.738	-0.070	0.050	-0.038	0.447	-0.135	0.060	0.003
Surfactant doses (n)	0.474	0.307	-0.443	1.391	0.299	0.575	-0.758	1.357	0.005
Post-natal steroids (y/n)	1.031	0.341	-1.107	3.169	0.325	0.808	-2.318	2.967	0.000
Sepsis (n)	1.540	0.107	-0.337	3.416	1.412	0.218	-0.851	3.676	0.015
Respiratory admission (y/n)	0.758	0.284	-0.637	2.153	0.551	0.544	-1.248	2.349	0.004

Table E16. Neonatal factors influencing ventilation heterogeneity in preterm adolescents and young adults. *p<0.05.

	Negative Binomial Univariate Regression Analysis				Negative Binomial Multi-variable Regression Analysis			
	IRR	p-value	95% CI Lower	95% CI Upper	IRR	p-value	95% CI Lower	95% CI Upper
Subpleural opacities								
Antenatal Steroids (y/n)	1.066	0.824	0.606	1.877				
Birth weight z-score	1.134	0.316	0.887	1.450				
Gestation Age (w)	0.855	**0.001***	0.777	0.941	0.955	0.634	0.792	1.153
IMV (d)	1.014	**0.012***	1.003	1.025	0.998	0.817	0.977	1.019
Supplementary O2 (d)	1.008	**<0.001***	1.003	1.012	1.005	0.267	0.996	1.014
CPAP (d)	1.014	0.092	0.998	1.031	0.998	0.843	0.975	1.020
Surfactant doses (n)	1.416	**0.008***	1.096	1.829	1.242	0.135	0.935	1.649
Post-natal steroids (y/n)	1.379	0.182	0.861	2.208	0.857	0.630	0.457	1.606
Sepsis (n)	1.799	**0.011***	1.142	2.834	1.346	0.257	0.805	2.249
Respiratory admission (y/n)	1.326	0.199	0.862	2.040	1.190	0.459	0.751	1.886
Hypoattenuation – Inspiration								
Antenatal Steroids (y/n)	1.000	1.000	0.000	0.000				
Birth weight z-score	1.933	**0.020***	1.110	3.366				
Gestation Age (w)	0.909	0.286	0.764	1.083	0.951	0.834	0.594	1.522
IMV (d)	1.004	0.655	0.985	1.024	0.962	0.105	0.917	1.008
Supplementary O2 (d)	1.007	0.109	0.999	1.015	1.018	0.066	0.999	1.037
CPAP (d)	1.001	0.961	0.973	1.029	0.975	0.256	0.934	1.018
Surfactant doses (n)	3.272	**0.004***	1.457	7.350	2.931	**0.006***	1.352	6.356
Post-natal steroids (y/n)	1.309	0.554	0.536	3.195	0.923	0.906	0.245	3.486
Sepsis (n)	0.280	**0.047***	0.079	0.985	0.191	**0.023***	0.046	0.796
Respiratory admission (y/n)	3.675	**0.009***	1.388	9.731	2.511	0.091	0.864	7.300
Hypoattenuation – Expiration								
Antenatal Steroids (y/n)	1.571	0.128	0.878	2.814				
Birth weight z-score	1.023	0.855	0.805	1.300				
Gestation Age (w)	0.929	0.102	0.851	1.015	0.961	0.652	0.809	1.142
IMV (d)	1.005	0.306	0.995	1.016	0.990	0.315	0.969	1.010
Supplementary O2 (d)	1.004	0.096	0.999	1.008	1.002	0.698	0.993	1.010
CPAP (d)	1.009	0.277	0.993	1.024	1.001	0.928	0.980	1.022
Surfactant doses (n)	1.173	0.190	0.924	1.489	1.079	0.572	0.829	1.405
Post-natal steroids (y/n)	1.443	0.121	0.908	2.294	1.482	0.192	0.821	2.677
Sepsis (n)	1.453	0.104	0.926	2.278	1.359	0.241	0.814	2.270
Respiratory admission (y/n)	1.182	0.438	0.775	1.804	1.145	0.557	0.728	1.801
Peribronchial thickening								
Antenatal Steroids (y/n)	1.235	0.640	0.510	2.988				
Birth weight z-score	1.160	0.410	0.815	1.651				
Gestation Age (w)	1.069	0.323	0.936	1.221	1.275	0.176	0.897	1.813
IMV (d)	1.002	0.807	0.987	1.017	0.978	0.163	0.949	1.009
Supplementary O2 (d)	1.005	0.151	0.998	1.011	1.015	**0.030***	1.001	1.028
CPAP (d)	0.928	**0.002***	0.886	0.973	0.902	**0.005***	0.838	0.970
Surfactant doses (n)	1.111	0.571	0.773	1.596	1.322	0.230	0.838	2.084
Post-natal steroids (y/n)	1.858	0.072	0.947	3.646	3.144	**0.043***	1.038	9.521
Sepsis (n)	0.967	0.926	0.480	1.948	0.970	0.952	0.358	2.628
Respiratory admission (y/n)	4.009	**<0.001***	1.890	8.505	4.054	**0.003***	1.597	10.290

Total Score								
Antenatal Steroids (y/n)	1.349	0.252	0.808	2.254				
Birth weight z-score	1.116	0.321	0.899	1.386				
Gestation Age (w)	0.908	**0.024***	0.835	0.987	0.976	0.769	0.829	1.149
IMV (d)	1.008	0.118	0.998	1.018	0.989	0.238	0.971	1.007
Supplementary O2 (d)	1.006	**0.006***	1.002	1.010	1.005	0.179	0.998	1.013
CPAP (d)	1.007	0.362	0.992	1.021	0.996	0.695	0.977	1.016
Surfactant doses (n)	1.281	**0.027***	1.028	1.596	1.194	0.152	0.937	1.521
Post-natal steroids (y/n)	1.440	0.094	0.940	2.206	1.229	0.467	0.705	2.144
Sepsis (n)	1.478	0.064	0.977	2.235	1.240	0.368	0.776	1.980
Respiratory admission (y/n)	1.391	0.094	0.946	2.047	1.262	0.270	0.835	1.908

Table E17. Neonatal factors as risks ratios for lung structure abnormalities in preterm adolescents and young adults. *p<0.05.